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Capsule Retention Caused by Cryptogenic Multifocal Ulcerous Stenosing Enteritis

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ABSTRACT

Introduction
Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) is a rare illness. Capsule retention (CR) has been reported in a few cases of CMUSE.

Methods
We present four cases of CMUSE with CR. None of the patients showed any symptoms or signs of small bowel obstruction before capsule endoscopy (CE). All patients denied a history of non-steroidal anti-inflammatory drugs intake, radiotherapy treatment or abdominal surgery.

Results
CE disclosed circumferential stenosis with or without ulcers in the small bowel, some accompanied by mucosal oedema, white spots and nodules. All patients underwent an elective surgery to remove the retained capsule and resect the lesions.

Conclusion
CE plays a positive role in diagnosing CMUSE. CE findings are as important as CR to alert for the diagnosis of CMUSE.

Keywords
Capsule endoscopy; capsule retention; small bowel; cryptogenic multifocal ulcerous stenosing enteritis

List of abbreviations
CR, capsule retention; CE, capsule endoscopy; CMUSE, cryptogenic multifocal ulcerous stenosing enteritis; CT, computed tomography; WBC, white blood count; PLT, platelet; IL, intestinal lymphangiectasia

INTRODUCTION
Capsule retention (CR) remains a major concerning complication of capsule endoscopy (CE), since it can potentially lead to acute small bowel obstruction and/or surgical intervention(1). Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) is a rare illness with unclear aetiology. CMUSE is characterised by unexplained superficial ulcers, thickened submucosa of the small bowel, and no biological signs of systematic inflammation(2). Diagnosis of CMUSE is very difficult and is based on history, clinical features, computed tomography (CT)/magnetic resonance enteroclysis, enteroscopy, and histology of the small bowel(3). CR has been reported in a few cases of CMUSE(2).

Here, we present a case series of CMUSE with CR. The diagnostic criteria for CMUSE were based on the previous study(4,5): 1. unexplained small bowel strictures; 2. superficial ulcer in the mucosa and submucosa; 3. chronic or relapsing ulcerative stenosis and abdominal pain; 4. no signs of systemic inflammation; and 5. persistent and occult blood loss from the gastrointestinal tract except during bowel rest or the postoperative period. CR was defined as having a CE remain in the digestive tract for a minimum of two weeks, or the capsule remaining in the bowel lumen unless direct medical, endoscopic, or surgical intervention was instituted(6). None of the patients showed any symptoms or signs of small bowel obstruction before CE. All patients denied a history of non-steroidal anti-inflammatory drugs intake, radiotherapy treatment or abdominal surgery. Surgical intervention was used to remove the retained capsule. All patients gave informed consent.
before CE.

CASE PRESENTATION

Case 1

A 60-year-old man was admitted to the department of Gastroenterology, with the main complaint of intermittent melena for 36 years, during which his haemoglobin dropped to ~2 g/dL, requiring repeated blood transfusions. He had a past history of recurrent cerebral infarction. White blood count (WBC), platelets (PLT), C-reactive protein, haemoglobin and serum albumin were 2.89 × 10⁹ /L, 86 × 10⁹ /L, 0.39 mg/L, 8.1 g/dL and 3.7 g/dL, respectively. Repeated upper and lower endoscopies, and abdominal CT were all normal initially. Bone marrow showed iron-deficiency anaemia. Recently, upper endoscopy showed portal hypertensive gastropathy. Enhanced abdominal CT showed splenomegaly and widening in the portal vein. CE disclosed a significant stenosis in the ileum. Selective small bowel enteroclysis confirmed the CR after one week and disclosed multiple short segment strictures in the ileum (the narrow bowel was less than 5 mm in diameter). Then, the patient underwent laparoscopic surgery to remove the retained capsule. Intraoperative endoscopy disclosed local multiple circumferential strictures with/without superficial ulcers in the ileum. In addition, approximately 18 cm of the segmental small bowel was resected. The small bowel histopathology disclosed nonspecific small bowel inflammation and multiple superficial ulcers, and the patient was diagnosed as CMUSE. The hepatic histopathology of liver biopsy confirmed the diagnosis of idiopathic non-cirrhotic portal hypertension. The patient did not receive further treatment. During the follow-up of 18 months, the clinical symptoms were relieved, and haemoglobin was elevated to approximately 13.0 g/dL.

Case 2

A 32-year-old man was admitted to the department of Lymph Surgery, with the main complaint of intermittent diarrhoea accompanied with lower extremity oedema for 13 years, aggravated with haematochezia for 3 years. WBC, PLT, haemoglobin and serum albumin were 6.06 × 10⁹ /L, 475 × 10⁹ /L, 6.0 g/dL and 1.9 g/dL, respectively. Abdominal CT disclosed splenomegaly and cholecystolithiasis. Direct lymphangiography showed malformation of the thoracic duct, drainage of double venous angle, and outlet obstruction of the thoracic duct. CE was then performed, which revealed mucosa oedema, white spots and nodules (dilated lacteals) in the small bowel,
accompanied by multiple ulcers and significant narrowing in the ileum. One month later, CR was confirmed by an abdominal X-ray. A laparoscopic surgery was performed to remove the retained CE, and approximately 70 cm of the ileum was resected. The gross specimen showed dilated proximal bowel segment, and multiple ulcers with strictures. Microscopically, superficial and non-granulomatous ulcers, and submucosal lymphatic dilatation were observed. The histological examination was suggestive of CMUSE with intestinal lymphangiectasia (IL). A low-fat diet including medium-chain triglycerides was instituted. During the follow-up of 2 months, diarrhoea, oedema, and haematochezia were all alleviated. However, one year later, these symptoms recurred, and the level of serum albumin had dropped to 1.8~2.0 g/dL.

**Case 3**

A 29-year-old woman, who had suffered from lower extremity oedema for 3 years, aggravated with diarrhoea and iron-deficiency anaemia for 6 months, was admitted to the department of Lymph Surgery. WBC, PLT, haemoglobin and serum albumin were 3.22×10⁹/L, 380×10⁹/L, 5.5 g/dL and 1.2 g/dL, respectively. Intestinal protein loss imaging indicated protein loss in the ileum. Then, CE showed white spots and nodules, mucosal oedema, and white coating, with segmental narrowing in the ileum. Direct lymphangiography showed obstruction of the thoracic duct. A following thoracic duct-left transverse jugular vein anastomosis was performed. Then, a low-fat diet including medium-chain triglycerides was instituted along with counselling at follow-up. Three months later, haemoglobin and serum albumin were 8.0 g/dL and 2.6 g/dL, respectively. In addition, abdominal CT showed splenomegaly and the retained capsule. A laparoscopic surgery was performed, which disclosed multiple strictures with ulcers in the ileum, and approximately 170 cm of the ileum was resected. The histopathology was suggestive of CMUSE with IL. The patient was lost to follow-up.

**CASE 4**

A 20-year-old woman had suffered from iron-deficiency anaemia for 16 years, growth retardation for 12 years, and intermittent abdominal distension and lower extremity oedema for 7 years. The patient had primary amenorrhea without secondary sex characters. Her height was 150 cm, and her weight was 35 kg. The lowest haemoglobin and serum albumin were 3.4 g/dL and 1.3 g/dL, respectively. WBC, PLT, and serum immunoglobulin G were 6.5 × 10⁹/L, 191 × 10⁹/L and 3.7 g/L,
respectively. Direct lymphangiography disclosed thickening and outlet obstruction of the thoracic duct with left subclavian and cervical ramus drainage. Then, the patient underwent surgery of the thoracic duct, to remove the outlet adhesion and to ligate the reflux branch. Colonoscopy revealed no colorectal abnormalities. Abdominal CT disclosed splenomegalhy. CE showed mucosal oedema, and a circumferential ulcer with stenosis in the ileum, and CR happened. A laparoscopic surgery was performed 6 months later, which showed segmental strictures and multiple ulcers in the ileum, and approximately 200 cm of ileal segment was removed. The histological examination was suggestive of CMUSE with IL. Then, a low-fat diet including medium-chain triglycerides was instituted. During the follow-up of over 7 years, the symptoms relieved, her height increased to 167 cm, and her weight was 55 kg.

The clinical characteristics and CE findings of this case series are summarized in Table 1. The representative images are shown in Figure 1.

DISCUSSION

A case series of CR caused by CMUSE was described. None of the patients had symptoms or signs suggesting small bowel obstruction, although they presented a retained CE. A retained capsule is an important clue alerting the physician to this possible diagnosis. Finally, all patients underwent elective surgery to remove the retained capsule, resect the small bowel lesions and confirm the diagnosis of CMUSE. Common causes for small bowel ulcers are Crohn’s disease and nonsteroidal anti-inflammatory drug enteropathy. Rare causes are autoimmune disease, neoplasm, vascular diseases, and nontuberculous infections(7). The morphology and histology of small bowel ulcers cannot provide a reliable differentiation in all cases. Small bowel ulcers and stenosis in CMUSE are nonspecific. The depth of the ulcers is restricted to the mucosa or submucosa, and they never extend to the proper muscular layer. The mucosal lesions are characterised by infiltration of plasma cells, lymphocytes, and eosinophils. In the histology, the margin of the ulcer is clearly demarcated by the surrounding villous mucosa(3,4). We have to include clinical features and histology to make a definitive diagnosis. When CE is performed in patients with provisional diagnosis of small bowel stenosis, the patency capsule can be used to evaluate the patency of the small bowel and avoid the risk of CR(8,9). However, patency capsule was not available in our hospital.

According to the literature, only several cases of CMUSE with CR have been reported (with
described CE findings). These patients had an onset age from 3 to 27 years. CE findings and clinical characteristics are shown in Table 2(2,10,11,12,13,14,15,16,17,18). It took a long time to confirm the diagnosis of CMUSE from the onset. CE disclosed erosions, ulcers and stenosis in the small bowel with or without bleeding sign. Stenosis were located in the jejunum, the ileum, and both the jejunum and ileum. Except ulcers and stenosis, CE also disclosed mucosal oedema, and white spots and nodules, which supported the diagnosis of IL. In our case series, gastrointestinal bleeding, iron-deficiency anaemia, protein-losing enteropathy and growth retardation were the main complaints. Some rare diseases, such as idiopathic non-cirrhotic portal hypertension, IL, and obstruction of the thoracic duct, were combined. According to the previous literature, CMUSE has extra-intestinal symptoms that include malaise, oral aphthae, Raynaud’s phenomenon, joint pain, obstructive pulmonary syndrome, Sicca syndrome, polyarthritis, arterial hypertension, peripheral neuropathy, and atrial fibrillation(19,20).

According to the literature, most of the CMUSE patients underwent a surgery to remove the retained CE (Table 2). Moreover, after CR, acute small bowel obstruction happened in only one case(2). In our case series, surgical intervention was chosen to remove the retained capsule. Device-assisted enteroscopy was not performed to retrieve the retained capsule, because it was not considered indicated by surgeons or endoscopists. Due to no presence of small bowel lesions, glucocorticoids were not prescribed to the patients before surgery. A low-fat diet including medium-chain triglycerides was added in cases with secondary IL; meanwhile, two of these patients underwent surgery to relieve the obstruction of the thoracic duct, and the outcomes varied.

In our cases 2, 3 and 4, CE disclosed mucosal oedema, white spots and nodules, and the surgical histopathology supported the diagnosis of IL. IL, a rare disease(21), is characterized by abnormal intestinal lymphatic system leading to the loss of plasma and thereby protein and lymphocyte loss into the gut(22). Small bowel obstruction and GI bleeding are the rare status(23). Here, all three patients showed hypoalbuminemia, lower extremity oedema, as a part of protein-losing enteropathy, and small bowel bleeding. Our CMUSE cases disclosed obstruction of the thoracic duct, which caused protein-losing enteropathy and IL. These findings indicate that some potential associations may exist in CMUSE and IL.

In conclusion, CE plays a positive role in diagnosing CMUSE. CE findings are as important as CR for alerting to the diagnosis of CMUSE. The association between CMUSE and IL deserves further
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1. Rondonotti E. Capsule retention: prevention, diagnosis and management. Ann Transl Med 2017;5:198. DOI: 10.21037/atm.2017.03.15


4. Singh A. Cryptogenic multifocal ulcerating stenosing enteropathy (CMUSE) and/or chronic non-specific multiple ulcers of the small intestine (CNSU) and non-granulomatous ulcerating jejunoileitis (NGUJI). Curr Gastroenterol Rep 2019;21(10):53. DOI: 10.1007/s11894-019-0721-6


Table 1. Capsule Retention in patients with Cryptogenic Multifocal Ulcerous Stenosing Enteritis in our case series.

<table>
<thead>
<tr>
<th>References</th>
<th>Sex/age (yr)</th>
<th>Onset age (yr)</th>
<th>Main complaint</th>
<th>Capsule endoscopic findings</th>
<th>Lesion location</th>
<th>Treatment</th>
<th>Follow-up time (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>M/60</td>
<td>24</td>
<td>Melena</td>
<td>Significant stenosis</td>
<td>Ileum</td>
<td>Surgery</td>
<td>18</td>
<td>Remission</td>
</tr>
<tr>
<td>Case 2</td>
<td>M/32</td>
<td>19</td>
<td>Diarrhoea, lower extremity oedema, haematochezia</td>
<td>Mucosal oedema, white spots and nodules (dilated lacteals), multiple ulcers and significant stenoses</td>
<td>Ileum</td>
<td>Surgery, low-fat diet including medium-chain triglycerides</td>
<td>17</td>
<td>Improved 2 months later, and recurred 1 year later</td>
</tr>
<tr>
<td>Case 3</td>
<td>F/29</td>
<td>26</td>
<td>Lower extremity oedema, diarrhoea, IDA</td>
<td>White spots and nodules, mucosal oedema, white coating, multiple ulcers with segmental narrowing</td>
<td>Ileum</td>
<td>Surgery, low-fat diet including medium-chain triglycerides</td>
<td>Lost to follow-up</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>Case 4</td>
<td>F/20</td>
<td>16</td>
<td>IDA, growth retardation, Abd distension, lower extremity oedema</td>
<td>Circumferential ulcer with stenosis, and mucosal oedema</td>
<td>Ileum</td>
<td>Surgery, low-fat diet including medium-chain triglycerides</td>
<td>87</td>
<td>Remission</td>
</tr>
</tbody>
</table>

Abd, abdominal; IDA, iron-deficiency anaemia
Table 2. Capsule Retention in patients with Cryptogenic Multifocal Ulcerous Stenosing Enteritis in the literature.

<table>
<thead>
<tr>
<th>References</th>
<th>Sex/age (yr)</th>
<th>Onset age (yr)</th>
<th>Main complaint</th>
<th>Capsule endoscopic findings</th>
<th>Lesion location</th>
<th>Treatment</th>
<th>Follow up time (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tao EW et al.²</td>
<td>F/43</td>
<td>23</td>
<td>Abd pain, IDA</td>
<td>Superficial and circular ulcers and stenosis, small bleeding spots on the surface of the ulcers</td>
<td>Ileum</td>
<td>Methylprednisolone (40 mg/day), Parenteral nutrition, Surgery</td>
<td>NA</td>
<td>Remission</td>
</tr>
<tr>
<td>Yang Y et al.¹⁰</td>
<td>F/29</td>
<td>13</td>
<td>Abd pain, melena, lower limbs edema</td>
<td>Multiple shallow ulcers and stenosis</td>
<td>Ileum</td>
<td>Surgery, Budesonide (9 mg/day) for 1 month, Methylprednisolone (40 mg/day)</td>
<td>12</td>
<td>Not improved</td>
</tr>
<tr>
<td>Kwon SO et al.¹¹</td>
<td>M/44</td>
<td>17</td>
<td>Abd pain, dizziness, IDA</td>
<td>Multiple mucosal erosions and shallow longitudinal ulcers</td>
<td>Jejunum and ileum</td>
<td>Surgery</td>
<td>6</td>
<td>Remission</td>
</tr>
<tr>
<td>Kijmassuwan T et al.¹²</td>
<td>F/10</td>
<td>3</td>
<td>IDA</td>
<td>Circumferential ulcerations, stenosis and bleeding</td>
<td>Jejunum and ileum</td>
<td>Surgery, Prednisolone 2 mg/kg/day, Azathioprine</td>
<td>10</td>
<td>Weight gained</td>
</tr>
<tr>
<td>Name</td>
<td>Gender</td>
<td>Age</td>
<td>Symptoms</td>
<td>Lesions</td>
<td>Location</td>
<td>Treatments</td>
<td>mg/kg/day</td>
<td>Outcome</td>
</tr>
<tr>
<td>-----------------------</td>
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</tr>
<tr>
<td>Singh A et al.</td>
<td>M/40</td>
<td>17</td>
<td>Colicky pain, constipation, Abd distension, melena</td>
<td>Superficial ulcer and stenosis</td>
<td>Jejunum</td>
<td>Surgery, Hormonal therapy, Non-residual diet</td>
<td>144</td>
<td>Improved, Steroid-dependent</td>
</tr>
<tr>
<td>Tacheci I et al.</td>
<td>F/36</td>
<td>NA</td>
<td>Abd pain, diarrhoea, weight loss</td>
<td>Roundish, stellar ulcers and erosions, and stenosis</td>
<td>Jejunum</td>
<td>None (Not fit for surgery)</td>
<td>7</td>
<td>Died from sepsis</td>
</tr>
<tr>
<td>Sun YN et al.</td>
<td>F/28</td>
<td>22</td>
<td>IDA, incomplete small bowel obstruction</td>
<td>Multiple circular ulcers</td>
<td>Ileum</td>
<td>Surgery</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Zhang Y et al.</td>
<td>F/36</td>
<td>16</td>
<td>Abd pain, IDA</td>
<td>Multiple pleiomorphic ulcers and stenosis</td>
<td>Ileum</td>
<td>Surgery</td>
<td>24</td>
<td>Remission</td>
</tr>
<tr>
<td>Li N et al.</td>
<td>F/22</td>
<td>18</td>
<td>Abd pain, IDA</td>
<td>Multiple scarred ulcers and stenoses</td>
<td>Not mentioned</td>
<td>Single balloon endoscopy</td>
<td>3</td>
<td>Remission</td>
</tr>
<tr>
<td>Wu Y, et al.</td>
<td>M/30</td>
<td>27</td>
<td>Abd pain, diarrhoea</td>
<td>Multiple stenoses and ulcers</td>
<td>Ileum</td>
<td>None</td>
<td>4</td>
<td>NA</td>
</tr>
</tbody>
</table>

Aabd, abdominal; IDA, iron-deficiency anaemia; NA, none applicable
Figure 1. Capsule endoscopic findings: A, significant stenosis; B ~ C, circumferential ulcer; D, circumferential ulcer with significant stenosis; E, small bowel mucosal oedema, white spots and nodules (dilated lacteals). Selective small bowel enteroclysis in Case 1: F, retained capsule in the ileum; G, multiple short segment stenosis of the ileum with dilatation of the proximal small-bowel loop. H, intraoperative endoscopy confirmed the significant stenosis (the same lesion of A) in Case 1. I, surgical gross specimen disclosed multiple ulcers with strictures in Case 1. J ~ K, histopathology disclosed superficial ulcers, by infiltration of plasma cells and lymphocytes.